PAPERS AND ORIGINALS

Lithium and Pregnancy—I, Report from the Register of Lithium Babies

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Summary

We have collected information about 118 children born to mothers who were given lithium treatment during the first trimester of pregnancy. The data show that the risk of teratogenic effects is lower than one might have expected from some of the studies carried out on rats and mice; they do not answer the question of whether or not lithium is teratogenic in man. The data were collected retrospectively and therefore overestimate rather than underestimate the risk of teratogenicity.

Introduction

It has been known for many years that lithium (lithium salts, lithium ions) added to the medium surrounding eggs of sea urchins, snails, and other lower organisms may interfere with morphogenesis so that monsters are produced (Herbst, 1893; Schou, 1957). Teratogenic lithium effects have also been shown in mammals. Szabo (1970) administered lithium by gavage to pregnant mice and induced cleft palate in up to 30% of the young. Wright *et al.* (1971) gave lithium intraperitoneally to pregnant rats and found cleft palate in 39% of the young, external ear defects in 45%, and eye defects in 63%. Other studies with the same and different animal species (rabbits, monkeys) and with administration of comparable lithium doses in the drinking fluid, in the diet, intraperitoneally, or subcutaneously have failed to show teratogenic action of lithium (Bass *et al.*, 1951; Trautner *et al.*, 1958; Johansen and Ulrich, 1969; Johansen, 1971; Schlüter, 1971; Gralla and McIlhenny, 1972).

The prophylactic effect of lithium in recurrent manic-depressive disorder has been known for some time (Baastrup and Schou, 1967; Schou and Baastrup, 1967), and an increasing number of patients are being given lithium maintenance treatment. Among those treated are women in the fertile age range, and since some of these become pregnant the question arises whether lithium administration to pregnant women carries the same high risk of congenital malformations as that observed in some of the animal studies.

In order to detect such a lithium effect as soon as possible we began some years ago to collect information about children born of lithium-treated women. The information could have been collected in different ways. One way would have been to use a prospective procedure where a number of women given lithium during the pregnancy were followed and the outcome of their pregnancies recorded. Another way was to work retrospectively and record "lithium babies" (see below) as they came to the notice of the Register of Lithium Babies. We chose the latter procedure because it had the best chance of giving early warning if the risk of teratogenicity was as high as indicated by the studies of Szabo (1970) and Wright *et al.* (1971).

A warning of this kind did not emerge from the data. Since we have now recorded more than a hundred lithium babies, we feel the time has come to report our findings.

Procedure

The Register of Lithium Babies started on a Scandinavian basis, but soon reports also arrived from outside Scandinavia. During the past few years information has been collected in the United States and Canada.

The existence of the Register has been announced through notes published at intervals in psychiatric and general medical journals. These notes urged physicians to submit reports about lithium babies, normal or abnormal, that might come to their notice. A "lithium baby" was defined as a child born of a woman who had been treated with lithium during the first trimester of pregnancy. Congenital malformations were defined as macroscopic abnormalities of structure attributable to

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faulty development and present at birth (McKeown and Record, 1960).

Results

The information submitted to the Register by the end of November 1972 is given in table I. Out of the 118 children reported five were stillborn and seven died within the first week of life; six of these 12 children were malformed. The total number of malformed children was nine. There were two children with Down's syndrome.

The Register has been in closer contact with Scandinavian physicians than with physicians outside Scandinavia. Since this might affect the submission of information, the reports from the two regions are presented separately.

Most of the malformations were serious and led to death shortly after birth (table II); the cardiovascular system was involved in six of the nine cases.

TABLE I—*Information Obtained from Reports to the Register of Lithium Babies by End of November 1972. Lithium Treatment had in All Cases Been Given during First Trimester of Pregnancy, in Most Instances Throughout the Trimester, in Some Instances during Only Part of it. Many of the Women Continued Taking Lithium Throughout Entire Pregnancy*

	All Reports	Reports from Scandinavia	Reports from Countries Outside Scandinavia
No. of infants reported	118	78	40*
Liveborn	113	73	40
Stillborn	5†	5	0
Died within one week after birth	7‡	2	5
Died two weeks after birth	1	1	0
Malformed	9	3	6
Down's syndrome	2§	0	2
Jaundice	2	1	1
Goitre	1	1	0
Perinatal asphyxia	1	0	1
"Floppy" at birth	2	0	2

*13 from Europe outside Scandinavia, 20 from U.S.A., 6 from Canada, and 1 from Australia.
†One of these was malformed and appears also in that group.
‡Five of these were malformed and appear also in that group.
§Both mothers were in their late thirties.

Discussion

The information was collected retrospectively, and one must therefore expect an over-representation of abnormalities among the reports. A lithium baby is more likely to be recognized as such and reported to the Register if it is stillborn or malformed or dies soon after birth than if it is alive and normal in every respect. Little attention may be paid to drugs taken during the pregnancy by mothers of normal and healthy children, whereas the birth of an abnormal child almost certainly leads to inquiries on this point. Incomplete and selective reporting is therefore probable. In our material there is a much higher frequency of congenital malformations among the reports from countries outside Scandinavia than among those from the Scandinavian countries. Since, as indicated above, the contact with physicians outside Scandinavia has been less close than with those inside Scandinavia, reports from the former are more likely to be incomplete and selective than reports from the latter.

It is accordingly likely that the frequencies of stillbirth, congenital malformations, and other anomalies in our material are higher than the true frequencies among children of lithium-treated women, and it is unlikely that they are lower. We are therefore on safe ground when we compare the frequency of malformations in our material with the frequency found in the studies of Szabo (1970) and Wright *et al.* (1971). The comparison shows that the risk of malformations among children of women given lithium during pregnancy is much lower than that indicated by the animal studies. Whether the risk is the same as or higher than the risk among children of women not given lithium we cannot tell. To answer that question one must use a different procedure.

The aim of the Register of Lithium Babies was to give early warning if the risk of teratogenic effects was as high in women as it was in some of the studies carried out in rats and mice. A large number of reports have now shown that it is not. Two of us (Schou and Villeneuve) feel that the Register has hereby accomplished its task and have now stopped collecting information about lithium babies. The two other authors (Goldfield and Weinstein) continue to collect the information. Future reports about lithium babies should be addressed to: The Lithium Baby Register, Langley Porter Neuropsychiatric Institute, 401 Parnassus Avenue, San Francisco, California 94122, U.S.A.

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TABLE II—*Information About the Malformed Children*

Case No.	Birth Date	Other Drugs during Pregnancy	Sex and Weight (g)	Malformation	Child's Fate	Report from:
1	9/3/68*	No information	F. Unknown	Coarctation of the aorta	Malformation corrected with surgery	U.S.A.
2	22/5/69	No information	M. 2,800	High intraventricular septal defect	Died on day 4	U.S.A.
3	23/8/69†	Chlorpromazine, diuretics	F. 3,080	Stenosis of aqueduct with hydrocephalus, spina bifida with sacral meningomyelocele, bilateral talipes equinovarus with paralysis	Unknown	Canada
4	28/9/69	None	M. 3,500	Unilateral microtia	Developing normally at age 3 apart from the malformed ear	Denmark
5	?/2/70	Haloperidol, nortriptyline, barbiturates, and others	Unknown, Unknown	Mitral atresia	Was operated on, died soon after	U.S.A.
6	23/2/71	None	F. 3,050	Cardiac malformation of Ebstein type	Died few days after birth	U.S.A.
7	28/9/71	No information	M. 2,200	Single umbilical artery, bilateral hypoplasia of maxilla	Died five hours after birth	Canada
8	22/2/72	Amitriptyline	F. 3,420	Cardiac malformation of Ebstein type	Died day after birth	Denmark
9	23/5/72	None	F. 2,200	Atresia of tricuspid valve	Stillborn	Denmark

*Reported by Lewis and Suris (1970). †Reported by Vacaflor *et al.* (1970) and Aoki and Ruedy (1971).